REMARKS

Claims 94, 97-100, 105, 108-111, 122, 123, 125, 126 and 158 were pending. Upon entry of this Amendment, claims 165-201 will be pending.

Claims 94, 97-100, 105, 108-111, 122, 123, 125, 126 and 158 are canceled herein. New claims 165-201 are submitted herein, basis for which can be found throughout the specification, drawings and claims as originally filed. The new claims find basis, for example, in original claims 105 and 125; Figures 7 and 8; and pages 21, 22, 24, 25 and 92-101 of the specification. No new matter has been added to the claims. The claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action. Applicant reserves the right to file subsequent applications claiming the canceled subject matter.

REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claim 122 is rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Claim 122 is canceled herein, rendering the rejection moot.

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 94, 97-103, 105, 108-111, 123, 125, 126 and 158 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking written descriptive support in the application. The Office Action asserts Applicant has provided no specific direction where support can be found for any particular limitations of the claims as amended and thus concludes the claims contain new matter. Applicant respectfully traverses this rejection.

Claim summary

Claims 94, 97-100, 105, 108-111, 123, 125, 126 and 158 are canceled herein and claims 101-103 were canceled in the Amendment filed June 3, 2005, rendering the rejection moot as it pertains to these claims.

New claim 165 and new claim 184 are, respectively, directed to a method of activating a double-stranded RNA nuclease comprising contacting the nuclease with a double-stranded RNA; and a method of detecting a double-stranded RNA nuclease in a sample, comprising contacting

the sample with a double-stranded RNA, wherein cleavage of the double-stranded RNA indicates the presence of a double-stranded RNA nuclease. The double-stranded RNA of the claimed methods comprises a first oligonucleotide and a second oligonucleotide, wherein at least one of the oligonucleotides has at least four consecutive 2'-hydroxyl ribonucleosides and at least one modified nucleoside. The oligonucleotides of the double-stranded RNA are hybridized to each other, but are not covalently linked. New dependent claim 166 specifies that activation of the double-stranded RNA nuclease results in cleavage of the double-stranded RNA.

New claims 167-183 and 185-201, directly or indirectly dependent from claims 165 and 184, further specify: the modified nucleoside or nucleosides increase resistance of the oligonucleotide to single-stranded nucleases and/or increase the affinity of the oligonucleotide to the other oligonucleotide; at least one modification is 2'-methoxy, 2'-fluoro, 2'-O-methoxyethyl or a phosphorothioate internucleoside linkage; the first and second oligonucleotide each have at least four consecutive 2'-hydroxyl ribonucleosides; the 2'-hydroxyl residues of the first and second oligonucleotide have phosphodiester linkages; the 2'-hydroxyl residues of the first and second oligonucleotide have phosphorothioate internucleoside linkages; the 2'-hydroxyl residues of the first oligonucleotide have phosphodiester linkages and the 2'-hydroxyl residues of the second oligonucleotide have phosphorothioate internucleoside linkages; the residues flanking the 2'-hydroxyl ribonucleosides of the first and second oligonucleotides have phosphorothioate linkages; the flanking residues of at least one of the oligonucleotides further comprises 2'-methoxynucleosides; the flanking residues of each of the oligonucleotides further comprises 2'-methoxynucleosides; at least one of the oligonucleotides comprises at least eight consecutive 2'-hydroxyl ribonucleosides; each of the oligonucleotides comprises at least eight consecutive 2'-hydroxyl ribonucleosides; each oligonucleotide is about 17 to about 20 nucleoside subunits in length; each oligonucleotide is 17 subunits in length; and each oligonucleotide is 20 subunits in length.

The claims are adequately described

Compliance with the written description requirement requires that the specification "must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, [the

inventor] had possession of *the invention*. The invention is, for purposes of the written description inquiry, whatever is now *claimed*." *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (emphasis added). The current claims are directed to a method of activating a double-stranded RNA nuclease or a method of detecting a double-stranded RNA nuclease in a sample using the double-stranded RNA compounds described in the specification.

The application provides more than adequate written descriptive support for the methods as claimed. A method of activating a double-stranded RNA nuclease using a double-stranded RNA is described in detail in Example 27, beginning on page 92 of the specification. The Example describes detecting double-stranded RNA nuclease activity by contacting a double-stranded RNA with rat liver homogenates. Activation of the double-stranded RNA nuclease is indicated by cleavage of the double-stranded RNA. The double-stranded RNAs are comprised of a sense oligonucleotide and an antisense oligonucleotide. The sense oligonucleotide comprises a region of 2'-hydroxyl residues with phosphodiester linkages, flanked by ribonucleosides with phosphorothioate linkages or 2'-methoxynucleosides with phosphorothioate linkages. The antisense oligonucleotide comprises a region of 2'-hydroxyl residues with either phosphorothioate or phosphodiester linkages, flanked by 2'-methoxy residues with phosphorothioate linkages. The illustrative dsRNA compounds have a region of 8 or 9 consecutive 2'-hydroxyl ribonucleosides and a length of 17 or 20 nucleoside subunits. The Example clearly states the oligonucleotides used for activation and detection of the double-stranded RNA nuclease were modified to distinguish double-stranded nuclease activity from single-stranded nuclease activity. Thus, the oligonucleotides comprise at least one modification to increase resistance of the oligonucleotide to single-stranded nucleases.

A method of detecting the presence of a double-stranded RNA nuclease in a sample also is supported by the description of Example 27 described above. Furthermore, Example 28, beginning on page 99 of the specification, and Figures 7 and 8, provide a detailed description of a double-stranded RNA digestion assay as a means to detect double-stranded RNA nuclease activity.

Furthermore, the specification provides ample support for other elements of the claims. For example, page 21 of the specification describes oligonucleotides in which at least one of the

nucleoside subunits is modified to increase the binding affinity of the oligonucleotide to its complement. Page 22 continues by describing enhancing binding affinity of an oligonucleotide by incorporating modifications at the 2' position, including but not limited to, fluoro, lower alkyl substituents (e.g. 2'-methoxy) and polyethylene glycol substituents (e.g. 2'-O-$CH_2CH_2OCH_3$, also known as 2'-O-methoxyethyl). In particular, the specification describes the 2'-O-(methoxyethyl) modification as one which increases both affinity of an oligonucleotide for its complement and nuclease resistance of the oligonucleotide. Page 21 of the specification also describes oligonucleotides modified to increase resistance to nucleases. At pages 24-25, the specification describes oligonucleotides with phosphodiester or phosphorothioate linkages and oligonucleotides with three, four, five or more consecutively linked 2'-hydroxyl ribonucleosides. Original claims 105 and 125 also provide support for the claimed methods.

Thus, the specification, claims and drawings as originally filed provide written descriptive support for the claimed methods.

Rebuttal of Examiner's arguments

The Office Action alleges the claims contain new matter, stating the Examiner was unable to find support for a double stranded compound contacted with a target RNA for modification or modulation. Applicants respectfully submit the claims as amended do not require that a target RNA is modified or modulated, nor do they require that the double-stranded RNAs be complementary to a target. Thus, the pending claims do not contain new matter.

On page 4 of the pending Office Action the Examiner specifically notes that pages 90-94 of the specification describe the use of double stranded, chemically modified sense and antisense oligonucleotides in an assay to detect dsRNase activity in cellular extracts, but concludes there is no support in the specification or claims as originally filed for any methods of activating a nuclease activity within a cell with double stranded RNA. The Examiner further states the purpose of the examples was to isolate RNase activity from cellular extracts and it is unclear how this might be extrapolated to provide support for activating a dsRNase in a cell. As detailed above, the specification thoroughly describes activation of double-stranded RNA nucleases using RNA duplexes. Specifically, Example 27 details the use of double-stranded RNA compounds to

elicit activation of double-stranded RNA nucleases in tissue extracts. Regardless of the purpose of the Examples, which Applicant does not concede is solely to isolate RNase activity, the specification clearly describes how one can activate a double-stranded RNA nuclease in a sample by contacting the sample with the described RNA compounds, and detect such activation by determining whether the double-stranded RNA is cleaved. Furthermore, in order to isolate a dsRNase, one must first identify a cell, extract or other sample with double-stranded RNA nuclease activity, which requires activation of the nuclease. In addition, original claims 105 and 125 provide support for methods of activating a double-stranded RNA nuclease. Therefore, the specification does provide more than adequate support for methods of activating a nuclease with double stranded RNA.

Conclusion

In view of the arguments presented above, Applicant respectfully submits the application as originally filed provides a more than adequate written description for the methods as claimed. One of skill in the art, armed with the information provided in the specification, would have been able to use the claimed methods and would have understood the inventors to be in possession of the methods at the time the application was filed. Accordingly, withdrawal of the rejection under 35 U.S.C. §112, first paragraph is requested.

The Commissioner is hereby authorized to charge the amount of $905.00 for a 3 month extension in time for reply and RCE fee, small entity, to Deposit Account 50-0252, referencing the above named application. It is believed that no further fee is due. However, if an additional fee is due, the Commissioner is hereby authorized to charge the Deposit Account referenced above.

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Withdrawal of the pending rejections and reconsideration of the claims is respectfully requested.

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